Remarks

Amendments to the Claims

Claims 1-27 and 44 drawn to arsenic trioxide compositions have been cancelled without prejudice solely to facilitate prosecution, and with the right to pursue them in a divisional or continuation application. Cancellation of claims 6 and 44 moot any issue of double patenting.

Method claims 28-34, 38-43 and 45 have been amended to define the dosage administered orally as causing less prolongation of QT interval and ventricular tachycardia in patients as compared to patients treated with the same dose by intravenous administration. Support for this amendment is found at page 19, lines 24-29, and page 28, lines 1-3. See also paragraph 6 of the declaration submitted with this Amendment and discussion below. Claim 20 has also been amended to incorporate the purity of claim 30, amended to refer only to a higher purity.

The Claimed Invention

As previously discussed with the examiner, the invention includes the use of orally administered arsenic trioxide which is as efficacious as intravenous arsenic trioxide but much safer. The previously submitted Declaration clearly demonstrates how the peak plasma levels are different for intravenous versus oral administration (i.e., area under the curve is the same, but the peak is significantly lower with oral administration), and as a result, causes less prolongation of QT interval and ventricular tachycardia in patients as compared to patients treated with the same dose by intravenous administration. Prolongation of QT interval and ventricular

tachycardia is positively correlated with the peak plasma arsenic level rather than the total amount entering the body. The importance of plasma levels on toxicity is also noted at page 10, lines 17-26; page 18, lines 24-29.

The differences in peak plasma level for intravenous administration as compared to oral administration are clearly evident from Figure 2. The method for measuring and determining plasma concentrations is found in the application at page 18, lines 3-9. The comparison of intravenous and oral administration is described beginning at page 18, line 23, to page 21, Table 3, and Figure 2. Figure 2 shows the plasma levels over time for individual patients, treated initially with intravenous arsenic trioxide, then oral arsenic trioxide. The dark lines are plasma levels; the dotted lines are blood levels. In all cases the levels are lower following oral administration; in some cases substantially lower. It should also be noted, as described in the enclosed Declaration, that there is residual arsenic trioxide in the plasma from the intravenous administration, at the time the drug is orally administered, so the measured levels for the orally administered arsenic trioxide are actually lower.

The differences in plasma concentrations and the effect on cardiotoxicity as measured as prolongation of QT interval and ventricular tachycardia, is noted at the bottom of page 27 to 28.

Rejections under 35 U.S.C. § 112

Claims 2, 3, 9, 29-34, and 38-45 were rejected under 35 U.S.C. § 112, first paragraph. This rejection is respectfully traversed if applied to the amended claims. Claims 2, 3, 9, and 44 have been cancelled.

The examiner's position is that there is insufficient support for the limitation "less cardiotoxicity in the form of cardiac arrhythmias. While applicants and the undersigned disagree with this conclusion, the claims have been amended to utilize the explicit language in the application relating to prolongation of QT interval and ventricular tachycardia as discussed above, and its difference as compared to intravenous administration. Accordingly, not only did the inventors conceive the oral administration of arsenic trioxide to treat cancer, but they contemplated AND DEMONSTRATED in the application AS FILED, that the oral administration reduced side effects relative to intravenous administration. As demonstrated by the attached declaration and references enclosed therewith, the differences defined by the amended claims for oral administration are significant as compared to intravenous administration.

With respect to claims 28-30, the examiner's attention is drawn to the specification at page 11 which clearly contemplated oral dosage forms other than a solution. It is also clear that powder or other dry form for resuspension at the time of administration was contemplated, as well as tablets and capsules. It is well known that tablets are typically prepared by compression of dry powder. The specification also refers to the liquid solution only as the preferred embodiment, thereby implicitly stating that other forms such as those listed are considered useful, if not preferred.

Rejections under 35 U.S.C. § 102

Claims 1-3, 9, 28-34, 38-42, and 45 were rejected under 35 U.S.C. § 102(f) in view of Kumana CR, Au WY, Lee NS, Kou M, Mak RW, Lam CW, Kwong YL, Eur J Clin Pharmacol. (2002) 58(8):521-6. epub 2002 Oct 11 and Siu CW, Au WY, Yung C, Kumana CR, Lau CP, Kwong YL, Tse HF, Blood (2006) 108(1):103-6. These rejections are respectfully traversed in view of the accompanying Declaration under 37 C.F.R. 1.131. The declaration establishes that the other named co-authors are not inventors because they did not conceive or reduce to practice the claimed invention, although they did help conduct the studies and analyze the data.

Claims 1-3 were rejected under 35 U.S.C. § 102(b) as anticipated by Yamauchi, et al., Toxicology 34(2):113-121 (1985). Claims 1-3 and 9 were rejected under 35 U.S.C. 102(e) as disclosed by U.S. Patent No. 6,875,451 to Ellison, et al. These rejections are moot in view of the cancellation of the claims, however, applicants reserve the right to refile these claims without prejudice or admission that the claims are anticipated by the prior art.

Claims 1-3, 28-32, 38, 40 and 45 were rejected under 35 U.S.C. § 102(b) as anticipated by Kwong, et al., Blood 89(9):3487-3488 (1997). These rejections are moot as to claims 1-3.

Kwong, et al. discusses the historical administration of Fowler's solution to patients with leukemia. Fowler's solution is actually a one percent by weight potassium arsenite solution, formed from arsenic trioxide, potassium bicarbonate, and hydroxide or carbonate and water. Also known as arsenious acid, it is sometimes administered as arseniate of potash or See attached documents. There is no indication of what other materials may be in the solution, although

others are known to be included, whether or not the potassium arsenite is equivalent in dosage to arsenic trioxide, or for that matter, what kind of dose was administered. See the attached Declaration under 37 C.F.R. §§ 1.131 and 1.132.

Claims 28 and claims dependent thereon, require the arsenic trioxide to have a purity of at least 90%. This excludes the Fowler's solution, which is not arsenic trioxide, but a 1% potassium arsenite solution.

Rejections under 35 U.S.C. § 103

Claims 1-3, 5, 6, 9 and 44 were rejected under 35 U.S.C. § 103 as obvious over U.S. Patent No. 6,875,451 to Ellison, et al. in view of U.S. Patent No. 6,723,351 to Warrell, et al. This rejection is moot in view of the cancellation of claims 1-3, 5, 6, 9 and 44.

Allowance of claims 28-34, 38-43, and 45 is respectfully solicited.

Respectfully submitted,

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